Clinical Trial Simulations in the Critical Path Initiative and Regulatory Decision-Making

Clinical Trial Simulations:
Many Questions, Few Answers
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Drug Development Can Best Deliver New Products Into Markets By _____

Most PhRMA companies are aiming for annual real revenue growth of 5-8% through 2012

Meeting this goal would require companies to develop and introduce 2-9 new products annually

Between 2002-2007 the top 10 PhRMA companies have launched just 0.6 new products yearly

Attrition has decreased PhRMA companies overall success rate to 21.5%

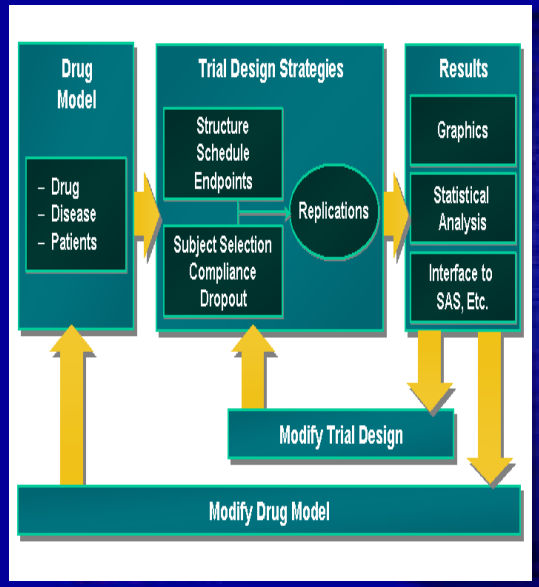
FDA will likely approve only 15-18 NMEs in 2007

Tufts University Center for the Study of Drug Development, 2007, and Institute for Alternative Futures, 2007

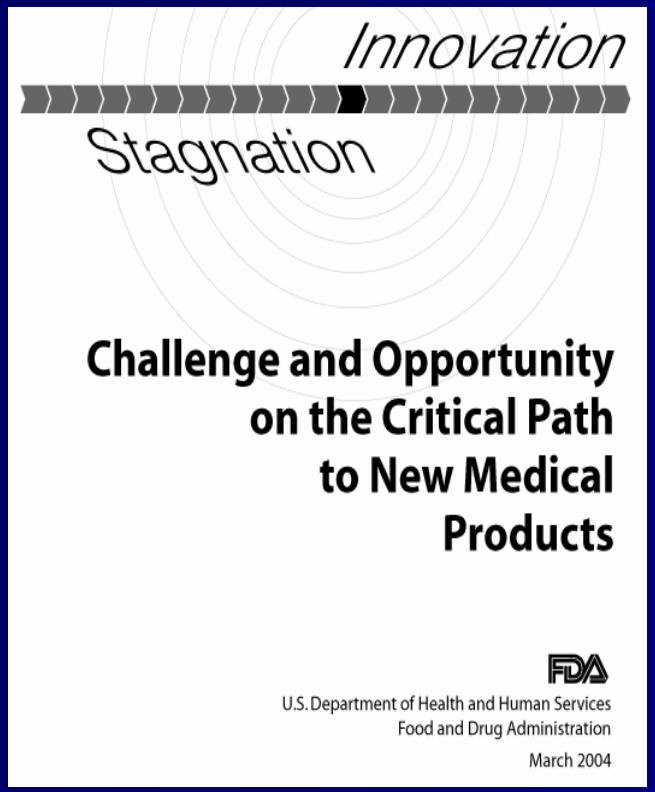
Drug Development……By Improving Efficiency and Multiplicity of Clinical Trials Designs

- Evidence of CTS found in very few NDAs but expansion of capabilities in industry increasing
- 40-45% of CTS projects in industry are found within phase 1 to 2A
- Demands for CTS in FDA has increased by 50% from 2006 to 2007
- 12 pharmacometricians active in CTS projects in FDA; most with < 10 yrs experience and 2/3 have no industry experience

THE TOP 10 QUESTIONS ABOUT CLINICAL TRIAL SIMULATIONS



10. What Does the Critical Path Say?



FDA scientists use, and are collaborating with others in the refinement of, quantitative *clinical trial modeling* using simulation software to improve trial design and to predict outcomes…..basis for systematizing information linked to outcome

www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

9. What Are CTS?

- Model development: E/R relationships (PK-PD) sometimes linked to disease-placebo progression models ~ co-variates, variability, placebo response etc

- Model execution: simulate clinical trials for the purpose of providing answers to specific questions ~ optimal dosing, probability of benefit or risk, sample size, effects of drop-outs and placebo response

- Execution analysis: visualize data, qualify biomarkers, sensitivity analysis of design features, inform decisions

8. Why Use CTS?

- To replicate the behavior of the modeled process to make testable predictions (e.g., about optimal dose)
- To build integrated models with more variables and co-variates (e.g., longitudinal change in biomarkers)
- Visualize the non-linear relationship between variables (e.g., exposure and benefit or risk)
- Standard framework for addressing a variety of questions which allows iteration on model design

7. What Is FDA's Commitment to CTS?

- CTS is a centerpiece of the critical path initiative and part of the future of drug development
- New human and computer resources have been provided to support this program
- Several quantitative disease models have been created to demonstrate commitment
- CTS is routinely used in EOP2A meetings and NDA review to leverage prior knowledge, frame discussion

6. What Are the Benefits of CTS?

- Gets review team speaking the same language, sharing insights and helps to build consensus
- Reduces data dimensionality to focus on which data sets decrease prediction errors
- Efficiency ~ models and simulations can be re-used and improved with regard to bias or uncertainty
- Decisions become more reproducible and subject to retrospective analysis ~ leveraged learning

5. How Is CTS Used in Regulatory Decisions?

Type of Decision	Role of CTS
Basis for Approval	Provide evidence of efficacy Quantitate probabilities of B/R Review and evaluate QT Evaluate failed BE studies
Labeling Claims	Formulate dosing recommendations Individualized doses in subgroups Assess drug-drug interactions Describe time course of endpoints
Designing Trials	Select range of doses for phase 3 trials Identify dose for optimal B/R Optimal sampling schemes in PK/PD Design stratification strategies
Setting Policy	Alternatives for endpoint analysis Set pivotal BE acceptance criteria Support guidance recommendations Claims for slowing disease progression

4. What Are the Attributes of a Successful CTS Experience?

- Top criteria is a biological theory behind the model, i.e., a modeled process with causal links
- Results of simulation aligned with results from studies within (i.e., internal validation) and across (i.e. external validation) NDAs
- Simulation scenario addresses relevant questions leading to actionable decisions (e.g., dosing)
- Interdisciplinary teamwork, quantitative skills (i.e., hypothesis and estimation) and good judgment

3. What Are the Barriers to Using CTS?

- Not having done the right experiment, not collecting the right data or not storing and archiving the data for efficient access (~ delays and less thinking time)
- Not having a gold standard for CTS, no systematic validation framework
- Stochastic properties (~ outcome probabilities) and operating characteristics (~ sensitivities) not established
- Not having evidence that CTS leads to a different decision than that arrived at in conventional way

2. What Are the Limitations of Using CTS?

- Predicting clinical outcomes for longer time periods than previously studied so B/R changes over time
- Asymmetry of data on benefit and risk makes integration and combined metrics difficult
- How to account for multiple efficacy endpoints used in registration trials
- Where and when to get “air time” early enough for sponsor to have meaningful discussions with FDA

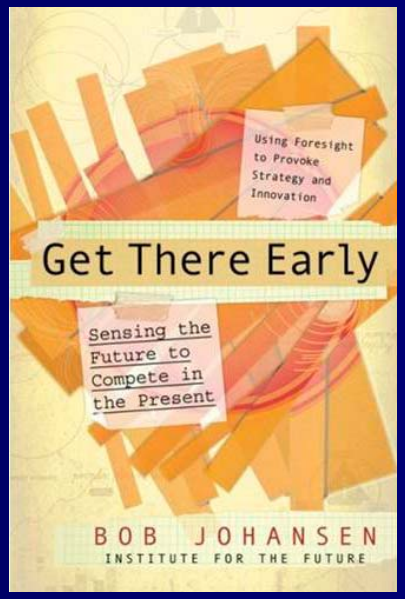
1. Has FDA Based Approvals or Label Claims on CTS?

- Yes, many times, in conjunction with other data

Scenario	Claim
Pediatric approval of trileptal	Monotherapy indication and dosing without efficacy trial
Subgroup approval of zoledronic acid	Approved dosing for renally impaired with clinical study
Risk management of busulfan in pediatric patients	Label recommendations for TDM without clinical study
Calcium channel blocker approvable because of dosing	Approval of more optimal dosing with new trials

Gobburu and Marroum, Clin Pharmacokin 2001, 40:883-892, Bhattaram et al, AAPS J 2005, 7:E503-E512, Bhattaram et al, Clin Pharmacol Ther 2007, 81:213-221

Take Home Message



Future risk or benefit can be predicted by statistical fitting of historical data and present data, and by clinical trial simulation.

But remember, we can't rely on models to do the thinking for us.

"Instruments, measures and analytics are great for flying airplanes but occasionally I find it useful to look out the window"

- Anonymous Airline Pilot